

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY




(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 25 APR 2005

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Applicant's or agent's file reference LP2009PC00	<b>FOR FURTHER ACTION</b> See Form PCT/IPEA/416	
International application No. PCT/EP2004/004127	International filing date (day/month/year) 19.04.2004	Priority date (day/month/year) 22.04.2003
International Patent Classification (IPC) or national classification and IPC C12P17/18, C07D498/22, C12R1/465		
Applicant LONZA AG et al.		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand  02.10.2004	Date of completion of this report  22.04.2005	
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Telephone No. +49 89 2399- <del>7150</del> 8547  	

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/EP2004/004127

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**Box No. I Basis of the report**

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1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4)
  - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

**Description, Pages**

1-9 as originally filed

**Claims, Numbers**

1-11 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	1-11
	No: Claims	
Inventive step (IS)	Yes: Claims	1-11
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	

2. Citations and explanations (Rule 70.7):

**see separate sheet**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
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**Re Item I**

**Basis of the report**

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Reference is made to the following documents:

- D1: EP-A-0 444 503 (SQUIBB BRISTOL MYERS CO) 4 September 1991 (1991-09-04)
- D2: EP-A-0 388 962 (SQUIBB BRISTOL MYERS CO) 26 September 1990 (1990-09-26)
- D3: EP-A-0 238 011 (KYOWA HAKKO KOGYO KK) 23 September 1987 (1987-09-23)
- D4: US-A-4 524 145 (MATSON JAMES A) 18 June 1985 (1985-06-18)
- D5: EP-A-0 575 955 (KYOWA HAKKO KOGYO KK) 29 December 1993 (1993-12-29)
- D6: US-A-4 107 297 (OMURA SATOSHI ET AL) 15 August 1978 (1978-08-15)

2. *Novelty and Inventive Step (Article 33(2)(3) PCT)*

- 2.1 The present application relates to a method of recovery of staurosporine from a fermentation broth comprising steps of
- (i) adding a water-miscible organic solvent A with the fermentation broth,
  - (ii) ultrafiltrating the dilute fermentation broth of step (i),
  - (iii) diafiltrating the retentate of step (ii) with a mixture of water and a water-miscible organic solvent B,
  - (iv) optionally adjusting the pH of the permeates to at least 8.5,
  - (v) concentrating the permeates of steps (ii) and (iii) until the water-miscible organic solvents are almost removed
  - (vi) adjusting the pH of the concentrate of step (v) to at least 8.5 (if necessary), and
  - (vii) collecting the precipitated staurosporine.

2.2 The prior art as disclosed in documents D1 to D6 uses solvents immiscible with water in order to extract staurosporine or analogues thereof from the fermentation broths. Even if water-miscible solvents are used as extractants, a transfer into an organic phase immiscible with water is performed. A further characteristic feature of the prior art methods is the compulsory use of chromatographic methods for further purification and isolation.

None of the prior art documents describes a process for the recovery of staurosporine possessing the technical features as claimed in the present application. The subject-matter of present claims 1-11 is therefore considered novel.

2.3 Any of the cited prior art documents D1-D3, D5 or D6 can be regarded as closest prior art. All methods therein disclosed use solvents immiscible with water as extractant and chromatographic steps in order to purify or to concentrate the desired product. The problem underlying the present application can be seen as to provide an alternative method for the recovery of staurosporine. The solution is a method comprising the steps (i) to (vii) (cf point 2.1 supra). The prior art gives no motivation to the skilled person dealing with the posed problem to deviate from the mainstream teaching of the prior art, i.e. to use a two-phase-extraction/chromatography combination. The presently claimed solution is insofar not obvious in the light of the prior art. Further advantages are the avoidance of, possibly, environmentally hazardous solvents and the use of large amounts of eluents (either solutions of salts or mixtures of organic solvents with water). Both the non-obviousness of the solution and the advantages over the prior art methods justify to acknowledge the presence of inventive step for the subject-matter of present claims 1-11.

3. Industrial applicability (Article 33(4) PCT)

The subject-matter of present claims 1-11 appear to comply with the requirements of industrial applicability as stipulated in Article 33(4) PCT.

Re Item VIII

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**Certain observations on the international application**

1. The term "almost completely removed" used in claim 1 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.